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EXAMINER	
FORD, ALLISON M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/582,342	BRANDS, RUDI	
	Examiner	Art Unit	
	ALLISON FORD	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *45-76* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *45-76* are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 9/23/2011 has been received and entered into the application file. No claim new claim amendments were made. Claims 45-76 remain pending in the instant application, all of which have been considered on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

RE Rejection of claims 45-59 and 63-67 under 35 USC 103(a) over Griffiths et al:

Applicants have traversed the rejection of record on the grounds that the Examiner has not established a *prima facie* case of obviousness. Specifically Applicants assert:

(A) Griffiths fails to teach or suggest a repeated discontinuous process. Applicants assert Griffiths teaches processes whereby either the volume (but not density) or the density (but not volume) of the cell culture is scaled-up, yet in both techniques the entire cell culture is transferred to the subsequent culture vessel, not merely a portion thereof, as is required by the instant claims (and as asserted to be obvious by the Examiner). Applicants reiterate that Griffiths 'passaging of the cells' does not inherently involve splitting the recovered culture into two portions and replating the two portion separately (Response at Pg. 4).

In response to (A), Applicants' arguments have been fully considered, but are not found persuasive. It is acknowledged that Griffiths does not teach splitting the harvested cell culture into two

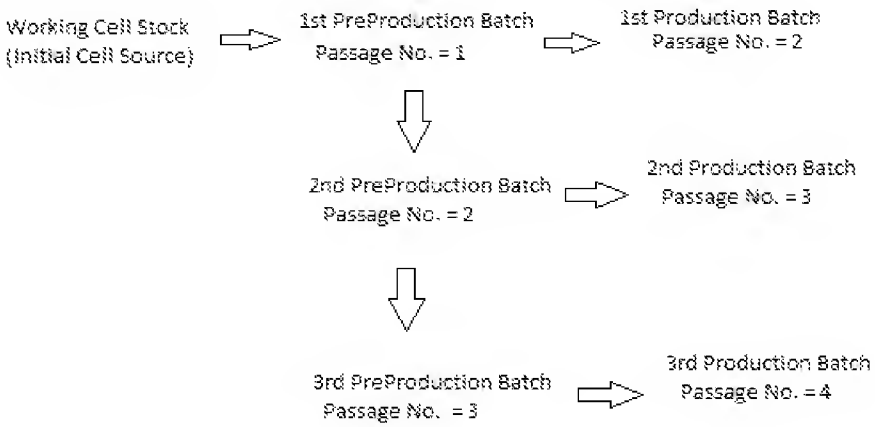
portions and replating each portion into separate cell culture vessels, and the rejection of record does not assert such. Rather the rejection of record acknowledges that Griffith does not teach splitting the recovered cell culture during the passaging step, but the rejection does state it would have been *prima facie* obvious to modify the method of Griffiths so as to involve such a splitting step. Noting that the method of Griffiths involves replating the *entire* recovered cell culture into the new culture vessel, the method of Griffiths exhausts the entire starting culture (which Applicants call the 'preproduction batch') in the first round, no subsequent 'production batches' can be derived from the starting culture, thus it has been submitted that it would have been *prima facie* obvious to modify the method of Griffiths to save a small portion of the starting culture (the 'preproduction batch') for future use, thereby saving money, as a new starting culture would not need to be purchased.

(B) Deficiencies of the cited references cannot be remedied by the Office's general conclusions about what is "basic knowledge" or "common sense". Applicants assert that it is improper to rely on 'common knowledge' as the principle evidence upon which a rejection was based.

In response to (B), it is submitted that the "principle evidence" is found in the teachings of Griffiths, it is the motivation and means by which to modify the method of Griffiths that is found in common knowledge. Furthermore, the Examiner has clearly supported the technical line of reasoning as to why one would have found the modification obvious. Applicants, however, have not specifically pointed out the supposed errors in the Examiner's action, such as stating why the noticed fact is not considered to be common knowledge or well-known in the art. Still further, the Examiner's assertion of such a modification being common knowledge within the art has been backed by the Board of Patent Appeals and Interferences.

(C) The Examiner has failed to establish that Griffith teach production batches having different passage numbers or teach that "the passage number of each production batch is between master cell bank and extended cell bank." Applicants assert that in conventional production of a biological occurs in production batches all having the same passage number. Applicants further assert that master cell bank (MCB) and extended cell bank (ECB) are not merely limits on a time range.

In response to (C), it is respectfully submitted that Applicants again are arguing differences between the disclosed method of Griffiths and the instant invention, whereas the instant rejection is based on the finding that the method of Griffiths *renders obvious* the instantly claimed invention. It has repeatedly been acknowledged that Griffiths does not teach splitting the recovered cell culture into two portions, using one portion as a production batch and saving the other for use as a preproduction batch, however, for the reasons discussed in detail below, such would have *prima facie* obvious. In the modified method the first production batch does have a different passage number than the second and subsequent production batches:



As can be seen from above (which is identical to the model defined at Pg. 4, lines 6-14 of the specification), in the *modified* method of Griffiths, wherein each 'preproduction batch' is split into two

portions (one for the 'production batch' and one for a subsequent 'preproduction batch') each of the *production* batches do have a different passage number.

Furthermore, with regards to Applicants' assertion that MCB and ECB do not merely define a time range, such is respectfully traversed. The instant specification does not put any actual limits on the "ECB" but rather only describes the ECB as being the passage limit at which cells still exhibit at least some of the same characteristics of the MCB (wherein MCB refers to the initial cell stock). However, without specific limitations regarding the ECB characteristics, the ECB is considered to be merely an upper limit of the passage numbers which cells may undergo and still produce the desired biological (in this scenario- the 'characteristic' which must be shared by the cells at the ECB and the MCB is 'production of the biological'). Once cells are no longer capable of producing the biological product, the cells are considered to have surpassed the ECB. Thus, MCB and ECB are properly considered time limits, or range limits, on the passage number of the cells, and wherein the characteristic defining the ECB is the ability to produce biological product, any cell which is still capable of producing the biological product will be considered to be within the MCB-ECB range. If Applicants intend to limit the term "ECB" by any specific characteristic or property of the cells, such must be claimed, as the specification does not provide a specific definition of such.

(D) That it would not have been obvious to simply apply the protocols of Griffiths to scaling up cultures of MDCK cells for the production of viruses because the art recognized that there were technical difficulties with scaling-up anchorage-dependent cells, such ask MDCK cells.

In response to (D), it is respectfully submitted that Griffiths is specifically directed to methods of scaling-up anchorage-dependent cells. Thus, while Griffiths initially recognizes that scale-up of anchorage-dependent has technical difficulties, the entire focus of Griffiths is how to overcome these

technical difficulties and successfully achieve scale-up of anchorage dependent cells. Thus the argument that scale-up of anchorage-dependent cells is not routinely possible in the art is not found persuasive, since the primary reference Griffiths particularly discloses means on how to do so.

(E) Finally, that the proportion of cell culture to be transferred in each step is not a result effective variable.

In response to (E) it is respectfully submitted that though Griffiths does not teach or suggest that the proportion of cells transferred to the production batch versus the proportion saved for use as a subsequent preproduction batch is a result effective variable, one having ordinary skill in the art will readily recognize that these proportions clearly are result effective. Specifically, one having ordinary skill in the art of cell culture for production of biological products will understand that the total amount of biological product which will be produced from a cell culture will directly depend on the number of cells in the cell culture, considering each cell is capable of making X amount of product, then the total amount of product which will be produced will be (number of cells in batch) x (X), assuming growth conditions are optimal. Thus, in modifying the method of Griffiths as suggested below, one would want to maximize the proportion of cells provided to each 'production batch' (in order to optimize the amount of product produced) while retaining just enough cells to support a subsequent 'preproduction batch'. Applicants have not provided any evidence or reasoning as to the criticality of the claimed ratios, thus the rejection of record stands.

Claims 45-59 and 63-76 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (Scale-up of Suspension and Anchorage-Dependent Animal Cells in Basic Cell Culture Protocols, Edited by Pollard et al. Humana Press Inc., 1997).

Griffith et al disclose methods for scaling-up cultures of anchorage-dependent cells for the production of biological products, comprising inoculating cells onto a substrate, such as a roller bottle or microcarrier beads, culturing the cells until they reach confluence, removing the culture media, rinsing the cells with PBS, adding trypsin to the cell culture to release the cells from the substrate, harvesting the released cells, diluting the harvested cells in fresh medium and passaging the cells (i.e. re-plating at least a portion of the cells) (See Griffiths et al, Section 3.2 "Anchorage-Dependent Culture" Pgs 65-71; especially Section 3.2.1.1.1 "[Roller Culture] Procedure" (at Pg. 67), Section 3.2.1.2.1 "[Glass Bead Immobilized Beds] Procedure" (at Pgs. 67-71) and Section 3.2.1.3.2 "[Microcarrier Culture] Procedure" (at Pg. 70-71)). The initial cell culture of Griffith et al reads on what Applicants are calling the 'preproduction batch', the passaged cells (re-seeded cells) read on what Applicants are calling the 'production batch', as the biological product will ultimately be produced and recovered from these cells.

Griffith et al differ from the instant invention in that, while they disclose harvesting and passaging the cells of their 'preproduction batch', they do not explicitly state the harvested cells are split into at least two portions, wherein a first portion of the cells are replated as a seed for a subsequent 'preproduction batch', and a second portion of the cells are transferred and used as a 'production batch' specifically for the production of biological products, which Applicants are calling a 'repeated discontinuous process'.

However, it is maintained that splitting the harvested cells into two portions, replating the first portion of the cells as a seed for subsequent 'preproduction batches', and transferring the second (larger) portion of cells for use as a 'production batch' for production of biological products produced by the cells (i.e. performing a repeated discontinuous process), would have been routinely performed by one of ordinary skill in the art. The person of ordinary skill in the art, being a cell biologist having experience in maintaining cell cultures, will understand that, in standard cell culture procedure, the cell culture is harvested, and only a portion thereof is replated into each new culture vessel, in this manner, the culture is

split. Splitting is necessary to prevent senescence of the cells: once cells reach confluence, they generally stop, if the culture becomes overcrowded, the cells will die due to lack of space and nutrients; thus the culture is continually 'thinned' out in order to permit for continuation of the cell culture.

Therefore, when carrying out the protocol of Griffith et al, it would have been *prima facie* obvious to one having ordinary skill in the art to split the recovered cell culture into at least two portions, and passage (i.e. replate) the majority of the culture into a subsequent cell culture vessel for production of the biological product, and passage (i.e. replate) the smaller portion of the culture into a subsequent cell culture vessel which can be maintained as a future source of cells. One would have been motivated to split the culture as such in order to save money (by not needing to purchase a subsequent cell culture seed), and increase the amount of biological product which can ultimately be produced (as the initial culture is not exhausted after the first round of biological product production, but a small portion can be retained, passaged and expanded, so as to provide a cell source for future 'production batches'). One would have had a reasonable expectation of successfully carrying out this 'repeated discontinuous process' because the steps of splitting and passaging cell cultures, as well as steps for obtaining biological products from a 'production culture' were well known in the art (see, e.g. Griffith et al).

Griffith et al thus renders obvious a method comprising:

Inoculating the cells onto the substrate. Because the cells necessarily come from a previous cell source, the previous cell source reads on a 'working seed stock,' the working seed stock is considered to have a passage number of 0. By inoculating the cells onto the substrate the cells are passaged a first time, the cells, once present on the substrate, read on what Applicants' call a first 'preproduction batch,' the first pre-production batch has a passage number of 1 (as they have been passaged 1 time- from the working seed stock to the first culture vessel) (thereby meeting the limitations of claims 45 step (a), 50, 51, 64 step (a), 66 & 67). The substrate may be a roller bottle (solid support) or microcarrier beads (particulate matter) (thereby meeting the limitations of claims 54-56 & 68-72).

Culturing the 'preproduction batch' until it reaches confluence, at which point the culture media is removed, the cells are rinsed with PBS, trypsin (a proteolytic enzyme) is added in order to cause the cells to release from the substrate, and the cells are harvested (meeting the limitations of claims 52, 57-59, & 73-75).

Dividing the harvested cell culture into at least two portions and re-plating each portion into a subsequent cell culture vessel having an appropriate substrate (meeting the limitation of claim 45 step (b)). Each re-plated portion further cultured to expand the cell number (meeting the limitation of claim 46). The first portion is subsequently used for production of the biological product; as such the first portion is considered to read on 'a [first] production batch' (meeting the limitation of claim 45 step (c), 49 step (i), 64 step (b), and 65 step (a)). The second portion is subsequently used as a source of future production batches, and as such, the second portion is considered to read on 'a [first] subsequent preproduction batch' (meeting the limitation of claims 45 step (d), 49 step (ii), & 65 step (b)). Both the first production batch and the first subsequent preproduction batch have a passage number of 2.

When the 'first subsequent preproduction batch' reaches confluence, the method is then repeated- the culture media is removed, trypsin is added in order to cause the cells to release from the substrate, and the cells are harvested, again the cells are divided into at least two portions, each portion is re-plated into a subsequent cell culture vessel having an appropriate substrate. Again, the first portion is subsequently used for production of the biological product; as such the first portion is considered to read on 'a [second] production batch' (meeting the limitation of claim 45 step (e)). The second portion is subsequently used as 'a [second] subsequent preproduction batch' (meeting the limitation of claim 47). Each of the second production batch and the second subsequent preproduction batch have a passage number of 3; thus the second subsequent preproduction batch has a different passage number than the first production batch (the first production batch having a passage number of 2, see above) (meeting the limitation in claims 45 & 64

that "the cells of the at least one production batch in c) have a different passage number than the cells of the at least one subsequent production batch in e)').

With regards to the limitation in claims 45 & 64 that 'the passage number of each production batch be between master cell bank and extended cell bank' it is submitted that this range merely defines the time period (by passage number) during which cells are able to successfully produce a desired biological product; thus as long as cells are capable of producing the desired biological product, they are considered 'between MCB and ECB', one having ordinary skill in the art would readily recognize when the cells have reached a point of senescence at which the cell culture can no longer be employed. This is considered to meet the limitation of claims 63 & 76- in that the ECB would have been routinely 'fully characterized' by the person having ordinary skill in the art to determine when the cell line has exhausted its utility.

Furthermore, though Griffith et al is non-specific with regards to the type of anchorage-dependent cell as well as the biological product being produced, it is submitted that the teachings of Griffith et al are intended to be general, and thus are applicable to any well-known anchorage-dependent cell line which is capable of producing a desired biological product. MDCK cells (anchorage-dependent cells) are notoriously old and well known in the art for their use in culture to grow viruses (dating back to at least the 70s); therefore it would have been obvious at the time the invention was made that the protocols of Griffith et al were applicable to scaling-up cultures of MDCK cells for the production of viruses. Initially, though with regards to the production of viruses as the specific biological product, it is noted that the methods of Griffith et al and Pollard et al are applicable to all anchorage-dependent cell types. Furthermore, anchorage-dependent cells that are routinely cultured to product viruses are also known in the art. For example, MDCK cells are notoriously old and well known in the art for their use in culture to grow viruses (dating back to at least the 70s). Therefore it would have been obvious at the time the

invention was made to split and passage MDCK cells, per the repeated discontinuous culture process discussed above for the production of viruses, thereby meeting the limitations of claims 45-58 & 64-74.

Finally, the modified method of Griffith et al still differs from the method of instant claim 48 in that there are no teaching as to the specific proportion of the cell culture to be transferred in each step; however the difference between the proportions of the total cell culture allotted for production of biological product and for use as a subsequent preproduction batch would have been routinely optimized by one having ordinary skill in the art. The proportion of cell culture which is taken out for the production batch is a result effective variable, as the amount used for the production culture directly effects the amount of product which will be produced each round. It has been held "[W]here the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation" See *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus the limitation of claim 42, requiring transfer of 80 to 90% of the preproduction batch for use in preparation of at least one production batch, and retaining the remaining 10 to 20% for use as a seed for production of a subsequent preproduction batch, would have been *prima facie* obvious to one having ordinary skill in the art, absent evidence to the contrary (claim 48).

Therefore, the instantly claimed method is not considered to be patentable, as it was obvious to one of ordinary skill at the time the invention was made. One would have known how to culture anchorage-dependent cells to produce a biological product, as illustrated by Griffith et al and it would be well within the purview of the skilled artisan, and generally common sense, to maintain a portion of the cell culture during each split, to replenish the original culture and use to repeat the process, thereby prolonging the culture life and increasing the amount of culture which can be used to produce the desired product.

It is further pointed out that this rationale relies on common sense and the knowledge generally available to the skilled artisan must be taken into account; such may be taken into consideration as

rationale for rendering an invention patentable per the Supreme Court decision of KSR International Co vs. Teleflex Inc. Specifically, the Supreme Court held that "Variations of particular work available in one field of endeavor may be prompted by design incentives and other market forces, either in same field or different one, and if person of ordinary skill in art can implement predictable variation, 35 U.S.C. §103 likely bars its patentability; similarly, if particular technique has been used to improve one device, and person of ordinary skill would recognize that it would improve similar devices in same way, then using that technique is obvious unless its actual application is beyond person's skill, and court resolving obviousness issue therefore must ask whether improvement is more than predictable use of prior art elements according to their established functions." See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) at 1386.

RE Rejection of claims 45-76 under 35 USC 103(a) over Wiktor et al:

Applicants have traversed the rejection of record on the grounds that the Examiner has not established a *prima facie* case of obviousness. Specifically Applicants assert:

(A') The techniques used for culturing VERO cells are not equally applicable to MDCK cells, and that scale -up of cultures of anchorage-dependent cells was known to have technical difficulties, and thus was not routine.

In response to (A'), it is respectfully submitted that Applicants' assertion that scale-up of anchorage-dependent cell cultures was not routine in the art, but was known to have many technical difficulties, is not found persuasive in light of the fact that both Wiktor et al and Griffiths et al each particularly disclose detailed processes for the successful scale-up of anchorage-dependent cell cultures. While scale-up of anchorage-dependent cells is more difficult than scale-up of suspension cultures, both Wiktor and Griffiths disclose protocols to overcome these difficulties. Applicants have not actually

shown any reason why the reasoning that the methods of Griffiths and/or Wiktor would not be suitable for use with MDCK cells.

(B') The Examiner fails to establish that Wiktor, Griffiths and Shimizu teach " a repeated discontinuous process". Generally Applicants repeat the arguments discussed under (A) above, regarding the differences between the process of Wiktor and Griffiths and the process of the instant claims. Applicants further assert that Shimizu fails to cure the deficiencies because Shimizu is not directed to production of biological product from anchorage-dependent cells, and specifically not to production of viruses from MDCK cells.

In response to (B'), it is acknowledged that Wiktor is generally in line with the protocol of Griffiths, and neither of them specifically exemplify a 'repeated discontinuous process', however, for the reasons discussed previously, the method of Wiktor is considered to *render obvious* a repeated discontinuous process, see remarks in response to (A) above.

Furthermore, though Shimizu is not directed to production of biologicals from anchorage-dependent cells, their teachings are clearly directed to a repeated discontinuous process, and extoll the benefits of such. Thus, it is maintained as proper that the technique of Shimizu (which is a repeated discontinuous process) would be applicable to the method of Wiktor (and/or Griffiths) as the technique of Shimizu is an improvement over the 'base' method of Wiktor (and/or Griffiths). One could have thus applied the known 'improvement' (of Shimizu) to the 'base' method of Wiktor/Griffiths for the predictable results of increasing the overall yield of biological product in a set amount of time in the method of Wiktor/Griffith, as the method of Shimizu permits nearly continuous (repeated discontinuous) cultures to be expanded one after another in the same time period.

It is respectfully submitted that Applicants have only attacked the references individually, as opposed to considering the teachings of the reference as a whole, including the combinations/modifications suggested therefrom.

(C') The Examiner has failed to establish that Wiktor, Griffiths or Shimizu teach production batches having different passage numbers or teach that "the passage number of each production batch is between master cell bank and extended cell bank." Applicants assert that in conventional production of a biological occurs in production batches all having the same passage number.

In response to (C'), it is respectfully submitted that Applicants arguments are the same as presented in (C) above, and thus for brevity Applicants are respectfully directed to the corresponding response, noting the protocol of Wiktor is substantially in line with that of Griffiths, the explanation of passage number is identical with respect to Wiktor and Griffiths.

(D') The art teaches away from the claimed invention as scale-up of anchorage-dependent cells was recognized as having technical difficulties and Groner et al, in particular, teach away from scaling-up of anchorage-dependent cell systems for the production of biologicals.

In response to (D') it is initially noted that Groner et al is not relied upon in any of the rejections of record, and thus is only considered as an extra teaching available in the art (as opposed to a direct teaching away in the cited reference). Yet while Groner et al discourages scale-up of anchorage-dependent cells, it is again reiterated that each of Wiktor and Griffiths specifically teach methods for scaling up cultures of anchorage-dependent cells. Based on the explicit detailed disclosures of Wiktor and Griffiths on how to successfully scale-up anchorage dependent cell cultures for the production of

biologicals, it is respectfully submitted that such was feasible and is clearly taught. Thus there the argument that a non-cited reference 'teaches away' is not found persuasive.

(E') That Shimizu does not cure the deficiencies of Wiktor and Griffiths, specifically Applicants reiterate their arguments presented in (B') and (D') above, Regarding the deficiencies of Shimizu and 'teachings away' by Groner.

In response to (E'), as (E') is generally a repetition of arguments presented and addressed as points (B') and (D') above, for brevity, Applicants are respectfully directed to the corresponding responses above.

(F') That Applicants' method produces unexpected results, specifically that the method allows high through-put production since the up scaling route from WCS to production cells can be very much shortened and much less bioreactors are needed since parallel production lines are not needed anymore."

In response to (F') it is respectfully submitted that Applicants have not explained how their claimed method achieves the scale up route from WCS to production cells in a shorter time compared to the methods of the prior art. Applicants have not provided or referenced any factual evidence that supports the assertion of unexpected results, nor have they explained how the method as claimed correlates to the asserted 'unexpected results', thus this argument is not found persuasive.

(G') Finally, that the proportion of cell culture to be transferred in each step is not a result effective variable.

In response to (G') it is respectfully submitted that this argument is substantially identical to that described under (F) above, and thus for brevity, Applicants are respectfully directed to the corresponding response above.

Claims 45-76 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wiktor et al (US Patent 4,664,912), in view of Griffith et al (In Basic Cell Culture Protocols, 1997), and further in view of Shimizu et al (Biotechnology & Bioengineering, 1985).

Wiktor et al disclose a method for large scale production of rabies virus in VERO cells, for use in production of a rabies vaccine. Specifically Wiktor et al discloses obtaining VERO cell line ATCC-CCL 81, the cells are provided frozen in liquid nitrogen at the 124th passage; the cells are subsequently cultured and divided to yield working seed stocks (at the 136th or 137th passages); cells of one working seed stock are seeded into a first bioreactor (See Wiktor et al, col. 4, ln 38-60). In the bioreactor the VERO cells are cultured on dextran microcarrier beads at 37°C (See Wiktor et al, col. 5, ln 14-38). At the end of the growth period the VERO cells are enzymatically released from the microcarriers by 0.025% trypsin in sodium citrate; and the VERO cells are then re-seeded on microcarrier beads in a second, larger bioreactor under the same conditions; the process is repeated in progressively larger bioreactors until a desired volume, i.e. 1000 L, is reached (See Wiktor et al, col. 5, ln 38-52). Once the desired volume is reached, the cell culture is inoculated with a viral seed, grown to full volume, and virus is eventually produced and harvested (See Wiktor et al, col. 6, ln 10-62).

Wiktor et al differs from the method of the instant claims in that (1) they are directed to production of a virus from VERO cells, whereas the instant claims are limited to production of a virus from MDCK cells, and (2) they do not disclose subjecting the 'preproduction batch' to a repeated discontinuous process, whereby only a portion of the cells from the preproduction batch are used in the

preparation of the production batch, and the remaining portion of the preproduction batch is used as a seed for the preparation of at least one subsequent preproduction batch.

With regards to (1) the type of cells: it is submitted that both VERO cells and MDCK cells were notoriously well known at the time the invention was made, are both anchorage-dependent animal cells, and were both well recognized as suitable cell types for the production of viruses. Therefore, though Wiktor et al is directed to culture of VERO cells, the method of Wiktor et al is considered to be equally applicable to MDCK cells, at least in terms of the mechanics and general protocol. Specific modifications so as to address different nutritional needs of the individual cell lines would have been routinely addressed by artisans having ordinary skill in the field of cell culture. For purposes of this rejection, the teachings of Wiktor et al regarding culture of the cells on microcarrier beads, scaling up of the cell culture volume, transferring between bioreactors, and eventual inoculation with virus in order to produce the desired viral product from the cells, is equally applicable to MDCK cells as it is to VERO cells.

With regards to (2) the repeated discontinuous process: at the time the invention was made repeated batch cultivation procedures using multiple bioreactors were well known in the art and were recognized as having the potential to increase overall productivity of a biological product from a cell culture by minimizing overall lag time (i.e. time when no culture is producing biological product). Repeated batch cultivation procedures are considered to be the same as what Applicants are calling a 'repeated discontinuous process.' For example, Shimizu et al disclose repeated batch cultivation procedures using multiple bioreactors (fermenters). In the procedure utilizing two bioreactors: cells, intended for production of a biological product, are seeded into a first bioreactor and cultured, when the cells reach a desired concentration a fraction of the first batch culture is withdrawn and transferred to a second bioreactor (i.e. is transferred as a seed for the preparation of a second batch culture). Fresh medium is added to both the first and second bioreactor. The cell culture remaining in the first bioreactor is used for the preparation of at least one biological product, after harvest of the biological product, the

bioreactor is emptied. Meanwhile, the cell culture previously transferred to the second bioreactor as a seed for the preparation of a second batch culture, is cultured to yield a second culture batch. The process may then be repeated: when the cells in the second batch culture reach a desired concentration a fraction of the second batch culture is withdrawn and transferred back to the first bioreactor (i.e. transferred as a subsequent seed for the preparation of a third batch culture), and so on (See Shimizu et al, Pg. 745-747 "Repeated Batch Cultivation Using Two Fermentors" & especially Fig. 5 on Pg. 746).

The crux of the Shimizu method is that once a cell culture batch has reached a desired volume a fraction is withdrawn and used as a seed to start a subsequent cell culture batch, the remaining portion is exploited for production of the biological product. By repeatedly starting a new batch culture at the same time fermentation is initiated in the original batch culture, the lag phase of the new batch culture overlaps with the production phase of the original batch culture, thereby reducing the wait time (i.e. unproductive time) between production phases of subsequent batch cultures. In this manner the repeated batch cultivation procedures using more than one fermentor improves the overall efficiency (in terms of production of the biological product) of the system compared to a single fermentor system by reducing the wait time when no product is being produced [by any batch culture] (See Shimizu et al, Pg 754, "Discussion and Conclusions").

The method of Wiktor et al utilizes multiple bioreactors, and thus has the potential to operate on a repeated batch cultivation schedule as taught by Shimizu et al. Therefore, it is submitted that one skilled in the art would have been motivated to modify the method of Wiktor et al to function on a repeated batch cultivation schedule, using two or more fermenters, in order to eliminate the long period during which scale-up is affected. In the method of Wiktor et al, the culture is not inoculated with the viral seed until the full scale-up volume (i.e. 1000 L) is reached; thus, up until that point, no virus product has been recovered, thus the entire scale-up procedure is non-productive wait time. Furthermore, after inoculation and virus production and harvest, the method must be started over again, beginning from a new working

seed stock phial, and the long period of non-productive wait time is repeated. By modifying the method of Wiktor et al to operate on a repeated batch cultivation schedule (as taught by Shimizu et al), productivity rates would be enhanced because multiple batch cultures are continually being scaled-up, thus new batches will regularly be available for inoculation with virus and viral production.

One would have had a reasonable expectation of successfully modifying the method of Wiktor et al to operate on a repeated batch cultivation schedule because the modification involves the same culture conditions, techniques, and bioreactors as used in the original method of Wiktor et al. The difference in re-seeding of the cultures is clearly taught by Shimizu et al, and is well within the purview of one having ordinary skill in the art.

In employing the repeated batch cultivation schedule of Shimizu et al in the method of Wiktor et al, the method of Wiktor et al would comprise:

Seeding cells of a working seed stock into a first bioreactor containing dextran microcarrier beads and culturing the cells at 37°C until a desired concentration is reached (producing a first batch culture). The cells of the first batch culture are considered to read on a first preproduction batch as claimed. Please note the cells of the first batch culture (first preproduction batch) were derived from the working seed stock; the working seed stock had been passaged from the 124th passage to the 136th/137th passage, and thus the first preproduction batch was prepared from a working seed stock by at least one passage step. The cells of the first batch culture (first preproduction batch) have a passage number of 136/137- for simplicity & clarity in writing this rejection the cells will be considered to have a passage number of 137 (thereby meeting the limitations of claims 45 step (a), 50, 51, 53-56, 64 step (a), 66, 67 & 69-72).

Upon reaching confluence, enzymatically releasing the cells of the first batch culture (first preproduction batch) from the microcarriers by 0.025% trypsin in sodium (meeting the limitations of claims 52, 57, 58, 68, 73 & 74).

Re-seeding a first portion of the cells of the first preproduction batch onto microcarrier beads in a second, larger bioreactor. This first fraction of cells of the first preproduction batch will eventually be employed for the production of at least one virus, and thus is considered to read on the first production batch (thereby meeting the limitation of claims 45 steps (b) (noting the culture was necessarily divided to obtain two different fractions), 49 step (i), 65 step (a)). At the point of passage to the second bioreactor the first production batch has a passage number of 138.

Re-seeding a second fraction of the cells of the first preproduction batch cells onto microcarrier beads in the first bioreactor. This second fraction of cells of the first preproduction batch then becomes the seed for a second preproduction batch (thereby meeting the limitation of claims 45 step (d), 49 step (ii), 65 step (b)). The cells of this 'second preproduction batch' have a passage number of 138.

Fresh medium is added to both the first and second bioreactor and both cell culture batches are cultured at 37°C until the desired concentrations are reached. When the cells in the second bioreactor (i.e. the first production batch) reach appropriate concentration, they may be subsequently passaged to progressively larger bioreactors, as taught by Wiktor et al, until the batch eventually reaches a size appropriate for inoculation with a viral seed, and will be used for production of viruses (thereby meeting the limitation of claims 45 step (c), 49 step (i), 65 step (b), and 65 step (a)).

When the cells of the first production batch in the second bioreactor are recovered and passaged to progressively larger bioreactors, the process begins again: the cells are harvested from the first bioreactor (i.e. the second preproduction batch), divided, a first fraction re-seeded into the second bioreactor as a second production batch, and a second fraction re-seeded into the first bioreactor as a seed for a third preproduction batch (thereby meeting the limitations of claims 45 step (e), 47, 64 step (a) (noting all production batches technically originated from the original preproduction batch), & 65 step (a)) The second production batch and the third preproduction batch each have a passage number of 139

(meeting the limitation of claims 45 and 64 that "the cells of the at least one production batch in c) have a different passage number than the cells of the at least one subsequent production batch in e)").

With regards to the limitation in claims 45 & 64 that 'the passage number of each production batch be between master cell bank and extended cell bank' it is submitted that this range merely defines the time period (by passage number) during which cells are able to successfully produce a desired biological product; thus as long as cells are capable of producing the desired biological product, they are considered 'between MCB and ECB', one having ordinary skill in the art would readily recognize when the cells have reached a point of senescence at which the cell culture can no longer be employed. This is considered to meet the limitation of claims 63 & 76- in that the ECB would have been routinely 'fully characterized' by the person having ordinary skill in the art to determine when the cell line has exhausted its utility.

The modified method of Wiktor et al still differs from the method of instant claims 59 & 75 in that Wiktor et al does not teach treating the cells on the microcarriers with PBS and/or EDTA prior to exposure to trypsin, however, it is submitted that washing cells with PBS to remove serum-containing culture residue (as serum inactivates trypsin) was a routine step which would be recognized by one having ordinary skill in the art. Griffith et al is cited in support. Griffith et al provide a more detailed protocol on passaging anchorage dependent cells, and specifically instruct to perform a rinse with PBS prior to addition of trypsin (See Griffith et al, Pg. 67, "3.2.1.1. Roller Culture", step 6) (thereby meeting the limitations of claims 59 & 75).

The modified method of Wiktor et al still differs from the method of instant claim 48 in that there are no teachings in Shimizu et al as to the specific proportion of the cell culture to be transferred in each step; however the difference between the proportions of the total cell culture allotted for production of biological product and for use as a seed stock would have been routinely optimized by one having

ordinary skill in the art. The proportion of cell culture which is taken out as the seed is a result effective variable, as the amount withdrawn as a seed for the subsequent culture directly effects the amount of product which can be yielded by the retained production batch (the greater the proportion removed as the seed culture, the less amount of culture retained for product production (i.e. less product produced by that production batch)), and also directly effects the duration of the preparation of the next preproduction batch (the greater the proportion removed as the seed culture, the less time that will be required to grow the seed culture to the preproduction batch desired volume). It has been held "[W]here the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation" See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus the limitation of claim 42, requiring transfer of 80 to 90% of the preproduction batch for use in preparation of at least one production batch, and retaining the remaining 10 to 20% for use as a seed for production of a subsequent preproduction batch, would have been prima facie obvious to one having ordinary skill in the art, absent evidence to the contrary (claim 48).

The modified method of Wiktor et al still differs from the method of instant claim 60 in that Wiktor et al does not exemplify "parking" the cells after a desired cell volume of the preproduction batch has been reached. However, it is submitted that Wiktor et al does teach that the cell cultures may be lowered from the optimal culture temperature of 35-38°C to a temperature of between 25° and 33oC in order to permit survival of the cells in a slowed-down growth phase (See Wiktor et al, col. 3, ln 41-44). The step of lowering the temperature of the culture (at any point in the method, including during culture in any one of the scale-up bioreactors) is considered to read on parking the preproduction batch of cells (as the cell cultures in each of the bioreactors except for the final bioreactor are considered to be preproduction batches) at a certain passage by exposing the cells to an ambient temperature within the range of 25° to 33°C. One having ordinary skill in the art would have been motivated to park the cultured

cells by lowering the culture temperature in order to slow down the growth phase of the cells in the parked culture. While, overall, the method of Wiktor et al should comprise growing the cells as quickly as possible to maximize production of virus, at times there may be problems in the production line which would result in a back-up in upstream bioreactors, for example if one of the larger bioreactors breaks, or even if a worker is unable to cultivate or harvest the viral load in the ultimate production batch due to a schedule conflict, etc. In such cases the cell culture batches upstream of the problem would need to be parked (i.e. slow down the growth phase, while retaining viability of the cell culture) while the downstream problem is addressed. Therefore, one would be motivated to park the cells in any of the preproduction batches by the method suggested by Wiktor et al: lowering the culture temperature to between 25° and 33° C. One would have had a reasonable expectation of successfully parking the cell cultures based on the explicit teachings of Wiktor et al (claim 60). Furthermore, to restore normal growth rates after the problem is addressed, it is submitted that it would have been within the purview of one having ordinary skill in the art to simply raise the culture temperature back to the standard 35° to 38° C and passaging the cells as normal (which includes changing the culture medium) (claim 61).

Alternatively, if the problem in the production line is severe enough that it cannot be corrected in a reasonable amount of time, or if the production line was to be temporarily suspended, it would have been prima facie obvious to one having ordinary skill in the art to cryopreserve each of the cell culture batches (within all bioreactors) and then store the culture batches until production is resumed. Wiktor et al disclose means for cryopreserving cultures of cells involving sealing the cell cultures and deep freezing the cultures in liquid nitrogen (See Wiktor et al, col. 4, ln 45-62). Liquid nitrogen stores items at -186°C (its boiling point); therefore storage in liquid nitrogen reads on the step of storing the cell culture batches at a temperature of less than -80°C, in bulk. The cell cultures would be defrosted when the production line is up and running again to restore productivity (claim 62). One would have been motivated to store the cell culture batches in each of the bioreactors in liquid nitrogen during a prolonged pause period in

production so as to not waste the cells; clearly, if the cells can be stored and recovered, it would be financially desirable to store the cells as opposed to starting the scale up procedures anew. One would have had a reasonable expectation of successfully storing the cells and subsequently thawing them prior to future use because Wiktor et al report cell cultures can be expanded, subsequently frozen, and then subsequently thawed and used for production (as in their working seed stocks, derived from the master cell stock).

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or

claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

RE Rejection of claims 45-76 as being provisionally rejected under the provisions of obviousness-type double patenting over co-pending application 11/654,556:

(A") Applicants' have responded to the provisional obviousness-type double patenting rejection by asserting that none of the instant claims are obvious over any of the co-pending claims. Furthermore, Applicants have stated they will wait to take action until a notice of allowance is received in the co-pending application (i.e. request the rejection be held in abeyance).

In response, Applicants' response has been fully considered and is acceptable at this time, as no notice of allowance has been issued in the co-pending application, the rejection is still provisional. The rejection stands at this time, but will be reconsidered if a notice of allowance is mailed in the co-pending application. It is further noted that the rejection has been modified in order to reflect the amended claims in the co-pending application, however it is not a new grounds of rejection, but rather only a modification of the claim numbers due to amendment in the co-pending case.

Claims 45-76 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 46-77 of copending Application No. 11/654,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims recite each of the limitations of the instant claims, though not necessarily in a single claim, the fact that each of the limitations are taught within the same application renders the instant method *prima facie* obvious..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 10:00-7:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1653